It is perhaps not sufficiently realized that the majority of babies which die during forceps extraction are killed because the forceps blades are wrongly applied, the operator having omitted the preliminary step of rotating the occiput completely to the front. It would be an exaggeration to say that injuries such as facial paralysis and tentorial tears never occur when the blades are correctly applied over each maxilla, but I believe that such a statement would not depart far from the truth. It is always instructive to examine the baby's head after forceps delivery; too often the tell-tale marks make it disappointingly evident that the blades have been applied, not to the robust maxillae, but to the yielding brow and occipito-mastoid region; and from this fact one may deduce that dangerous compression of the cranial vault has taken place. It is not always easy to rotate completely the head which is in "deep transverse arrest," but with practice this manœuvre is usually successful, and by its accomplishment the chances of safe delivery of the foetus are greatly improved.

The Course of Labour and Diagnosis

I shall not do more than touch on diagnosis. Late engagement of the head and early rupture of the membranes in the absence of disproportion between the head and pelvis is an ominous sign. A foetal heart heard far out on the flank, or more especially one heard faintly over a wide area of lower abdomen, may help in diagnosis but must not be relied on.

The character of the uterine contractions is often peculiar. They are short, painful, and unaccompanied by bearing-down effort. It might be supposed that such ineffective contractions are the primary abnormality and the cause of the slow advance of the foetus, but I tend to the view that when the head descends into the occipito-posterior position the vagina is not evenly distended, and consequently the reflex which normally augments contractions and compels the patient to bear down is not evoked. I am always suspicious of the patient who, although she has started labour well, has made little or no advance over several hours, and about whom the nurse in charge querulously exclaims, "If only she would use her pains!" Such a patient should be carefully examined, and not infrequently it will be found that the foetal head has remained unrotated in the occipito-posterior position.

I have already referred to the frequency with which non-rotation of the head is associated with obstructed labour, yet in spite of the commonness of the condition many of these cases remain undiagnosed until too late. The chief reason for this is that the suture lines are obscured by an oedematous scalp; it is only by passing the fingers to a higher level and feeling the foetal ear that a certain diagnosis can be made. To do this an anaesthetic is necessary, and the whole hand suitably lubricated must be gently inserted into the vagina. Such an examination should always precede forceps delivery in any case of doubt. That grand old man of obstetrics Sir Halliday Croom used to speak of this procedure as the "trump card" of obstetrics. I cannot do better than end with his famous words, "Gentlemen, gentlemen, I pray beg each one of you, *when in doubt play trumps.*"

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INTERRUPTION OF EARLY PREGNANCY BY MEANS OF ORALLY ACTIVE OESTROGENS

BY

A. S. PARKES, Sc.D., F.R.S.

(From the National Institute for Medical Research, London)

E. C. DODDS, M.D., D.Sc., F.R.C.P.

AND

R. L. NOBLE, M.D.*

(From the Courtauld Institute of Biochemistry, Middlesex Hospital, London)

It was found many years ago that the injection of oestrogenic extracts after mating interfered with the establishment of pregnancy (Smith, 1926; Parkes and Bellerby, 1926), and subsequent work, including numerous experiments carried out with pure hormone substances, has amply confirmed this observation. Small doses of an oestrogen prevent the ova of mice from passing down the tube (Burdick and Pincus, 1935), while larger doses cause abnormal acceleration of transit (Burdick and Whitney, 1937). Both types of disturbance cause death of the blastocyst. In the rabbit the cleavage rate of the egg is not affected by the injection of oestrone after ovulation, but the embryos die; the maximum sensitivity to oestrone is on the third and fourth days after mating (Pincus and Kirsch, 1936; Pincus, 1936, may be consulted for further discussion).

The prevention of progestational changes in the uterus of the rabbit after ovulation, by injection of oestrogenic hormones, has been extensively studied by Courrier and his co-workers. Adequate doses of oestrone given in the early stages of the luteal phase will suppress endometrial proliferation and prevent implantation of the egg. The administration of oestrone after implantation has taken place causes death of the embryo. The rabbit is very sensitive up to the fourth day after mating, less so on the fifth and sixth, and more so again at the twelfth (Courrier and Kehl, 1932; Courrier and Reynaud, 1933, 1934).

The action of oestrone in inhibiting progestational changes in the uterus is well shown, and can be quantitatively assessed, by experiments on immature or ovariectomized test animals sensitized with oestrone and then injected simultaneously with progesterone and varying amounts of oestrone (Hisaw and Leonard, 1930; Allen, 1932; Robson, 1936; Zuckerman, 1937).

In view of these facts it is clearly of the greatest importance to know whether oral administration of oestrogens can be made effective enough to prevent or disturb implantation of the blastocyst. Recently a new derivative of oestradiol has been prepared by Inhoffen and Hohlweg (1938). This substance, ethinyl oestradiol, is reported to be seventeen times as active by mouth as oestradiol (Inhoffen, Logemann, Hohlweg, and Serini, 1938). Further, the new synthetic oestrogen, diethyl-stilboestrol, prepared by Dodds, Golberg, Lawson, and Robinson (1938), the biological properties of which have been described by Dodds, Lawson, and Noble (1938), is reported to be highly active by mouth. The capacity of these two substances, given orally, to suppress the progestational action of progesterone and to prevent the establishment of pregnancy has therefore been investigated.

* Leverhulme Fellowship, Royal College of Physicians of London.

Administration

The substances were fed to rabbits in propylene glycol solution, which was swallowed readily. Diethyl-stilboestrol was administered to the rats in oil solution by stomach tube under brief ether anaesthesia. The concentrations were so adjusted that the maximum daily dose was 1 c.cm.

Inhibition of the Effect of Progesterone on the Uterus of the Immature Rabbit

Immature female rabbits were sensitized with three doses of 50 I.U. (0.005 mg.) of oestrone according to the technique of McPhail (1934). They were then given a standard dose of 0.6 I.U. (0.6 mg.) of progesterone in oil solution over three days by subcutaneous injection, together with varying amounts of ethinyl oestradiol or diethyl-stilboestrol by mouth. It was found that total doses of 0.15 mg., 0.3 mg., and 0.75 mg. of the oestrogens very greatly decreased the progestational proliferation caused by the progesterone, while 1.5 mg. and 3 mg. abolished it. It was difficult to assess accurately the slight proliferation occurring with the medium doses of the oestrogens, but it seems that diethyl-stilboestrol is slightly less effective than is ethinyl oestradiol in suppressing progestational proliferation.

Inhibition of Implantation in Rabbits

Technique and Controls.—Adult rabbits which had been isolated for several weeks were mated, and most of them were laparotomized one to three days later to ascertain if ovulation had taken place. Of twenty-four so examined twenty-two were found to have ovulated. Of twenty mated rabbits which received no treatment, or only control propylene glycol by mouth during the first week, implantation took place in eighteen. The implantation rate, therefore, was good.

Oral Administration of Ethinyl Oestradiol.—Seven rabbits received ethinyl oestradiol during the first week after mating, and were killed and examined at from six to nine days *post coitum*, when progestational proliferation should have been well advanced. The details are given in Table I. The uteri of the four which were treated

TABLE I.—*Effect of Ethinyl Oestradiol by Mouth on Implantation in the Rabbit*

No. of Rabbit	Ethinyl Oestradiol given			Rabbit Killed, Days after Mating	Normal Implantations	Progestational Proliferation of Endometrium
	Days after Mating (inclusive)	Daily Dose in mg.	Total Dose in mg.			
DNT 20	5–6	0.25	0.5	9	2	Normal
DNT 19	5–6	0.25	0.5	9	2	,,
DNT 23	2–6	0.25	1.25	6	0	Slight
DNT 3	3–4	1	2	8	0	Some
DNT 22	2–6	0.5	2.5	6	0	Slight
DNT 6	2–7	0.5	3	8	0	None
DNT 5	2–7	1	6	8	0	,,

for five or six days showed little or no progestational proliferation, although the corpora lutea in the ovary seemed quite normal. The two larger doses had caused tremendous oedema and hyperaemia of the uteri. In the rabbit receiving two doses of 1 mg. the endometrium had proliferated, but the glandular development was poor for eight days after ovulation. There were no signs of pregnancy in these rabbits. In the two animals receiving doses of 0.25 mg. on the fifth and sixth days after mating, implantation had not been entirely inhibited, though the number of embryos (two) found in each was much below the number of corpora lutea, suggesting that there was partial failure. The results in general leave no doubt that ethinyl oestradiol by mouth is effective in preventing implantation after mating and ovulation.

Oral Administration of Diethyl-stilboestrol.—The results with diethyl-stilboestrol are given in Table II. It will be

TABLE II.—*Effect of Diethyl-stilboestrol by Mouth on Implantation in the Rabbit*

No. of Rabbit	Diethyl-stilboestrol given			Rabbit Killed, Days after Mating	Normal Implantations	Progestational Proliferation of Endometrium
	Days after Mating (inclusive)	Daily Dose in mg.	Total Dose in mg.			
DNT 41	3–7	0.5 (twice daily)	5	8	1	Good
DNT 42	3–7	0.5 (twice daily)	5	8	2	Subnormal
DNT 24	3–8	1	6	10	0	Good
DNT 25	3–8	1	6	10	0	Subnormal
DNT 28	2–7	1	6	9	0	,,
DNT 35	3–7	2	10	8	0	Very slight
DNT 38	3–7	2	10	8	0	Slight
DNT 39	3–7	4	20	8	0	,,
DNT 40	3–7	4	20	8	0	,,

seen immediately that 1 mg. daily given over a five-day period after mating does not entirely prevent the occurrence of normal implantations, while the endometrial proliferation is not seriously interfered with. A similar dose of ethinyl oestradiol caused profound uterine changes quite incompatible with implantation of blastocysts. With larger doses of diethyl-stilboestrol normal implantations were not found, but a total of 10 mg. was required before the progestational proliferation was mainly inhibited. Not until 20 mg. was given did the intense hyperaemia and congestion of the uterus appear which was found even with 3 mg. of ethinyl oestradiol. Both the microscopic and the macroscopic observations leave no doubt that diethyl-stilboestrol is effective in preventing implantation and progestational proliferation of the endometrium in the mated rabbit, but it is much less effective than ethinyl oestradiol. In several of the animals receiving the smaller doses of diethyl-stilboestrol there were nodules in the uterus which were obviously not normal implantations, and which seemed to consist of a decidual reaction with a degenerate vesicle. It is likely that a degree of inhibition of progesterone had been attained incompatible with the continued survival of the blastocyst, but inadequate to prevent decidua formation.

Inhibition of Implantation in Rats

Technique and Controls.—Female white Wistar rats weighing 150 to 250 grammes were segregated after detection of mating by the presence of a vaginal plug. Oral administration of diethyl-stilboestrol began one day later. The total dose was dissolved in 3 c.cm. of oil, and 1 c.cm. was given daily for three consecutive days. The animals were killed on the eighth day *post coitum*. Control animals received oil only.

Oral Administration of Diethyl-stilboestrol.—The results given in Table III showed that implantation occurred in eight of eleven control rats and in two of three receiving

0.001 mg. of the oestrogen. It occurred in only three of eleven rats receiving between 0.005 and 0.016 mg., and was completely absent in thirteen rats receiving larger

TABLE III.—*Effect of Diethyl-stilboestrol by Mouth on Implantation in Rats*

Total Dose gamma	No. of Rats	Pregnancy	Total Dose gamma	No. of Rats	Pregnancy
0	11	8	20	3	0
1	3	2	30	3	0
5	3	1	50	2	0
10	6	1	100	2	0
16	2	1	200	3	0

doses. It is thus evident that this new synthetic oestrogen given by mouth is highly effective in preventing implantation in rats.

Interruption of Established Pregnancy

Technique and Controls.—Fifteen rabbits were used for experiments on established pregnancy. A preliminary laparotomy under ether anaesthesia at eight to twelve days after mating was made in twelve of these to confirm the presence of normal implantation. Five of those laparotomized received control treatment with propylene glycol alone, and all were subsequently found to have normal foetuses.

Oral Administration of Ethinyl Oestradiol.—Six rabbits were treated with ethinyl oestradiol by mouth, beginning nine or ten days after mating, and were killed at twelve to fourteen days. The details are shown in Table IV. All

TABLE IV.—*Effect of Ethinyl Oestradiol by Mouth on Established Pregnancy in the Rabbit*

No. of Rabbit	Ethinyl Oestradiol Given			Rabbit Killed, Days after Mating	Condition of Embryos
	Days after Mating (inclusive)	Daily Dose in mg.	Total Dose in mg.		
DNT 17	9–10	0.1	0.2	13	2 normal conceptions; 5 resorbing
DNT 7	9–10	0.25	0.5	13	4 resorbing
DNT 8	9–10	0.25	0.5	13	9 „
DNT 15	10–11	0.25	0.5	14	8 „
DNT 10	8–9	0.5	1	12	7 „
DNT 2	9–11	0.5	1.5	13	2 „

the embryos in the rabbits receiving a total of 0.5 mg. or more were resorbed or undergoing resorption. In the remaining animal, receiving 0.2 mg., two live foetuses were found in seven implantation sites. Observations on the state of the resorbing conceptuses seem to agree substantially with those made by Courrier, and there can be little doubt that identical effects are produced by the injection of oestrone and the oral administration of ethinyl oestradiol.

Oral Administration of Diethyl-stilboestrol.—A rabbit receiving 1 mg. of this oestrogen on the thirteenth, fourteenth, and fifteenth days after mating was found on the seventeenth day to contain ten embryos, all being reabsorbed. A similar dose on the eleventh, twelfth, and thirteenth days, and half this dose on the tenth, eleventh, and twelfth days in other rabbits did not disturb pregnancy. It is evident, therefore, as in the work on implantation, that the denidatory effectiveness of diethyl-stilboestrol is much less than that of ethinyl oestradiol.

Discussion

The above results indicate that small doses of orally active oestrogen administered by mouth will prevent implantation of the blastocyst if given soon after ovulation, or may terminate established pregnancy. The effect is produced in what is essentially a physiological manner: the luteal phase of the cycle is suppressed, and another phase induced which, though not abnormal in itself, is unsuitable for the development of the embryo.

Everything we know about the menstrual cycle of primates suggests that its hormonal control is the same as in lower animals, and it is extremely probable that the factors governing the implantation of the fertilized egg are fundamentally similar in women and in lower animals. The experimental conclusions arrived at above should thus be applicable to women, though the fact that very large amounts of oestrogen are excreted by pregnant women makes it likely that the period during which oestrogen treatment might be effective would be relatively much shorter than in rabbits.

It would be unwise at the present juncture to make a comparison of the relative suitability of the two substances examined, or of other orally active oestrogens, for the purpose under consideration. Effectiveness in this kind of test must be greatly influenced by conditions of absorption from the alimentary canal, and these conditions certainly vary from species to species. It is difficult to predict what type of substance would be most effectively absorbed by mouth in women. Further, the intensive work at present being carried out on the artificial production of oestrogenic substances may well result in the production of a compound also active by mouth, but more effective in suppressing the tubal and uterine changes necessary for implantation of the fertilized egg than either of those so far examined.

Summary

Experiments have been carried out on the inhibition of implantation and the interruption of established pregnancy by the oral administration of two new oestrogens—ethinyl oestradiol and diethyl-stilboestrol. Both of these substances given by mouth inhibit the effect of progesterone and prevent implantation of the blastocysts in rabbits. Small doses of diethyl-stilboestrol prevent implantation in rats, while ethinyl oestradiol is highly effective in interrupting established pregnancy in rabbits.

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